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Applicant: Sloan-Kettering Institute For Cancer Research
1275 York Avenue
New York New York 10021(US)

(72)

Inventor: Watanabe, Kyoichi A.
28 Wilton Road
Rye Brook New York 10573(US)

(72)

Inventor: Matulic-Adamic, Jasenka
117 Carroll Avenue
Mamaroneck New York 10543(US)

(72)

Inventor: Price, Richard W.
31 Dobbs Terrace
Scarsdale New York 10583(US)

(72)

Inventor: Fox, Jack J.
424 South Lexington Avenue
White Plains New York 10606(US)

(74)

Representative: Patentanwälte Schulze Horn und
Hoffmeister
Goldstrasse 36
D-4400 Münster(DE)

(54)

Nucleosides of 5-monofluoromethyluracil and 5-difluoromethyluracil.

(57)

A method for synthesizing monofluoromethyl- and difluoromethyluracil nucleosides from the corresponding thymine nucleosides is developed. These compounds which contain a partially fluorinated methyl group at the C-5 position (a new class of nucleosides) are potential antiviral and/or anti-cancer agents. The major features of the preparative route involve bromination of suitably protected thymine nucleosides followed by fluoride treatment.

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10 Nucleosides of 5-Monofluoromethyluracil and
5-Difluoromethyluracil

The invention described herein was made in the course of
work under a grant from the U.S. Department of Health and
15 Human Services.

BACKGROUND

20 5-Trifluoromethyluracil was originally synthesized in
very low yield by a multistep procedure starting from
trifluoroacetone-cyanohydrin (Heidelberger, et al., J.
Am. Chem. Soc., 84, 3527 (1962); J. Med. Chem. 7, 1
(1964)). Later, this compound was prepared more con-
25 veniently from uracil-5-carboxylic acid by treatment
with sulfur tetrafluoride (Mertes, et al., J. Med.
Chem., 9, 876 (1964)). The 2'-deoxynucleoside, i.e., 1-
(2'-deoxy- β -D-erythropentofuranosyl)-5-trifluoromethyl-
uracil or F₃ TDR, was prepared by condensation of the
30 base and sugar halide in very low yield. (Heidelberger,
Progr. Nucleic Acid Res. Mol. Biol., 4, 1 (1965); Cancer
Res., 30, 1549 (1970)).

5-Difluoromethyluracil was also prepared but was found
35 to be extremely labile in neutral aqueous media (Mertes,
et al., loc. cit). No nucleosid containing this base has
been synthesized. Attempts to synthesize 5-monofluoro-

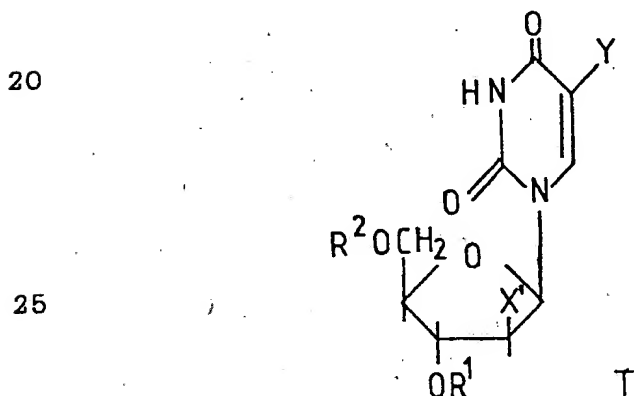
- 1 uracil have failed (Mertes, loc. cit). No 5-monofluoro-
methyluracil nucleoside is known.

Our theoretical considerations suggest that substitution
5 of the N-1 position of 5-(partially-fluorinated)-methyl-
uracils with an alkyl or sugar moiety should decrease
the lability of the fluorine in the heterocyclic base.
Therefore, nucleosides containing 5-(partially fluori-
nated) methyluracils should be obtainable by synthesis
10 from a preformed nucleoside.

SUMMARY

- 15 Nucleosides of the invention can be represented by
Formula I as follows:

Formula I



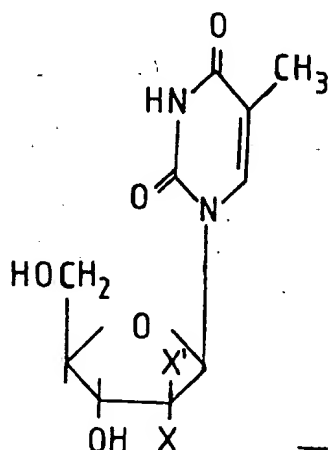
- 30 Wherein either X or X' is always H.
X or X' is H, OR³, or a halogen such as fluorine,
chlorine, bromine or iodine as well as pseudohalogen
such as lower alkylsulfonyl group of 1 to 5 carbons such
as methyl-, ethyl- propyl-, isopropyl-, butyl-, isobu-
35 tyl-, sec-butyl-, tert-butyl, and pentylsulfonyl or
arylsulfonyl such als benzene-, p-toluene-, p-nitro-
benzenesulfonyl grouping.

- 1 Y is monofluoromethyl (CH_2F) or difluoromethyl (CHF_2).
 2 R^1 , R^2 and R^3 are the same or different and are hydrogen
 3 or aryl groups of 1 to 20 carbon atoms such as formyl,
 4 acetyl, propionyl, isopropionyl, butyryl, isobutyryl,
 5 tert-butyryl, valeryl, pivaloyl, caproyl, capryl, lauryl
 6 , myristyl, palmityl, stearyl, arachidyl, stilligyl,
 7 palmitoyl, oleyl, linolenyl, arachidonyl and the like, or
 8 trisubstituted silyl groups such as tert-butyl-dimethyl-
 9 silyl, tert-butyldiphenylsilyl, dimethylphenylsilyl and
 10 the like.

DESCRIPTION OF INVENTION

- 15 The present invention relates to the novel class of
 nucleosides which contain 5-monofluoromethyluracil or 5-
 difluoromethyluracil as their aglycon. A further aspect
 of the present invention relates to processes for prepar-
 16 ing uracil nucleosides containing a partially fluori-
 17 nated methyl group at the C-5 position and intermediates
 20 useful therein.

The starting materials for the process of the present
 invention can be subsumed under general Formula II, as
 25 follows:



Formula II

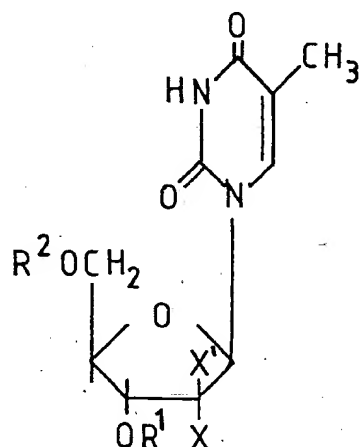
35

X or X^1 is hydrogen
 X or X^1 is as defined previously.

II

- 1 Nucleosides of Formula II are acylated with alkanolic acid chloride or alkanolic acid chloride or alkanolic acid anhydride in organic base such as pyridine or triethylamine. Acylation of Formula II nucleosides is also achieved with alkanolic acid chloride or alkanolic acid anhydride in aprotic solvent such as methylene chloride, chloroform, dichloroethane or tetrachloroethane in the presence of organic base such as pyridine, lutidine, collidine, triethylamine, N,N-diethylaniline, p-(dimethylamino)pyridine, 1,8-diazabicyclo(5,4,0)undec-7-ene or 1,5-diazabicyclo(4,3,0)-non-5-ene.

Upon completion of the reaction, the reaction mixture is quenched suitably, by adding excess alkanol such as methanol, ethanol, propanol and the like, to hydrolyze the acylating reagent. After concentration of the mixture, the acylated intermediates can be obtained in pure condition either by direct crystallization of the residue from various solvents or solvent systems, or by chromatography over a column of silica gel G60 using various solvent systems. The acylated intermediates



Formula III

III

- obtained by the above procedure can be presented under general Formula III, wherein
- X or X₁ is always hydrogen
- X or X₁ is OR₃, or a halogen such as fluorine, chlorine,

- 1 bromine or iodine as well as pseudohalogen such as lower
alkylsulfonyl group of 1 to 5 carbons such as methyl-,
ethyl-, propyl-, isopropyl, butyl-, isobutyl-, sec-
butyl, tert-butyl- and pentylsulfonyl or arylsulfonyl
5 such as benzene-, p-toluene-, p-nitrobenzenesulfonyl
grouping.
- ¹R, ²R and ³R are the same and are aryl groups of 1 to
20 carbon atoms such as formyl, acetyl, propionyl, iso-
10 propionyl, butyryl, isobutyryl, tert-butyryl, valeryl,
pivaloyl, caproyl, capryl, lauryl, myristyl, palmityl,
stearyl, arachidyl, stearyl, palmitoyl, oleyl,
linolenyl, arachidonyl and the like.
- 15 Nucleosides of Formula II are also converted into the
corresponding partially silylated intermediates by
treatment with trisubstituted-silyl chloride such as
tert-butyldimethylsilyl, tert-butyldiphenylsilyl or
dimethylphenylsilyl chloride in organic base such als
20 pyridine or triethylamine. Silylation of Formula II
nucleosides can also be performed with trisubstituted-
silyl chloride in aprotic solvent such as methylene
chloride, chloroform, dichloroethane, tetrahydrofuran,
dioxan, benzene, acetonitrile, ethyl acetate and the
25 like in the presence of organic base such as pyridine,
lutidine, collidine, triethylamine. N,N-diethylaniline,
p-(dimethylamino)pyridine, 1,8-diazabicyclo(5,4,0)undec-
7-ene or 1,5-diazabicyclo(4,3,0)non-5-ene. The silyla-
tion reaction is carried out at -40° to 174° C (preferably
30 from 20° to 30° C), in a period of from 1 hour to 6 days.

When the reaction is carried out without solvent, or in a
water-miscible aprotic solvent, the mixture is concen-
trated in vacuo, the residue dissolved in an aprotic
35 solvent such as methylene chloride, chloroform, benzene
or the like, and washed with water, dried over sodium
sulfate or magnesium sulfate and then concentrated in

- 1 vacuo. After the reaction is performed in an aprotic
solvent not miscible with water, the mixture is added
into cold water, the organic layer separated, dried over
sodium sulfate or magnesium sulfate, and then concen-
5 trated in vacuo. The residue is purified either by
direct crystallization or by chromatography on a silica
gel G60 column using various solvent systems.

The silylated intermediates can be subsumed under
10 general Formula III wherein:
X or X¹ is hydrogen.
X or X¹ is OR³, a halogen such as fluorine, chlorine,
bromine or iodine as well as a pseudohalogen such as the
lower alkylsulfonyl group of 1 to 5 carbons such as
15 methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-,
sec-butyl-, tert-butyl and pentylsulfonyl or arylsul-
fonyl such as benzene-, p-toluene-, p-nitrobenzenesul-
fonyl grouping.

20 Among R¹, R² and R³, one or two are trisubstituted-silyl
groups such as tert-butyldimethyl-, tert-butyldiphenyl-
or phenyldimethylsilyl groupings, and the rest are
hydrogen.

25 The intermediates of Formula III nucleosides are reacted
with 1 or 2 equivalents of bromine under ultraviolet
light irradiation in polyhalogenated carbon solvent such
as carbon tetrachloride at a temperature range of from
0° to 77° C in a period of from 1 to 6 hours. When 1
30 equivalent of bromine is used, 5-monobromomethyluracil
nucleosides (Formula I, Y = CH₂Br) are formed. Reaction
of Formula III intermediates with 2 equivalents of bro-
mine results in the formation of 5-dibromomethyluracil
nucleosides (Formula I, Y = CHBR₂).

35 Upon completion of the reaction, nitrogen gas is bubbled
through the mixture for a period of from 10 minutes to 1

1 hour (preferably 30 minutes), to remove hydrogen bromide
 which is produced during the bromination reaction. The
 mixture is then concentrated in vacuo to afford crude
 bromomethyluracil intermediates (Formula I, Y = CH₂Br or
 5 CHBr₂) which can be purified as a very unstable powder.
 More practically, the mixture can be fluorinated directly
 without purification of the bromomethyl-uracil inter-
 mediates. Thus, the crude intermediates are dissolved in
 an appropriate, aprotic solvent and a fluorinating agent
 10 is added. When silver fluoride is used as a fluorinating
 agent, acetonitrile is the preferred solvent. When
 tetrabutylammonium fluoride is employed as the fluorina-
 ting agent tetrahydrofuran is the more suitable sol-
 vent. Acetone is recommended when Amberlyst A-26 (F⁻) is
 15 used as the fluorinating agent.

The mixture is stirred vigorously at a temperature
 range of from -40° to 80° C (preferably from -10° to
 30° C), for a period of from 5 minutes to 5 hours. The
 20 mixture is filtered from insoluble materials and the
 filtrate is washed with water, dried over sodium sul-
 fate or magnesium sulfate, concentrated in vacuo, and
 the residue chromatographed over a column of silica gel
 G60 using various solvent systems, preferably n-hexane-
 25 ethyl acetate or a methylene chloride-tetrahydrofuran
 combination.

The free Formula I nucleosides wherein Y is CH₂F or CHF₂
 and R₁ and R₂ are hydrogen, is prepared from the corres-
 30 ponding acyl intermediates (Formula III, wherein Y is
 CH₂F or CHF₂, R₁ and R₂ are the same and alkonyl groups)
 by treatment with mineral acid in water or alkanol,
 preferably 1 % to 5 % hydrogen chloride in methanol.
 More preferably, the free nucleosides of Formula I are
 35 prepared from the corresponding partially silylated
 intermediates (Formula III, Y is CH₂F or CHF₂, R₁ and/or
 R₂ is/are trisubstituted silyl and X or X₁ is OH or

1 trisubstituted silyloxy group) by treatment with fluoride ion in an appropriate solvent, preferably with tetra-n-butylammonium fluoride in tetrahydrofuran.

5 The free nucleosides (Formula I, Y is CH_2F or CHF_2 , R^1 and R^2 are hydrogen) and their acylated analogs (Formula I, Y is CH_2F or CHF_2 , R^1 and R^2 are the same or different and alkanoyl) may be useful therapeutic agents exhibiting antiviral and/or anticancer activity, and may
10 be employed in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier which can be an organic or inorganic inert carrier material suitable for enteral or parenteral administration such as, for example, water,
15 gelatin, gum arabic, lactose, starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, petroleum jelly, etc. The pharmaceutical preparations can be made up in solid form (e.g., as tablets, dragees, suppositories or capsules), or in liquid form (e.g., as
20 solutions, suspensions or emulsions). The preparations may be sterilized and/or may contain adjuvants such as preserving, stabilizing, wetting or emulsifying agents, salts for varying the osmotic pressure, or buffers. Such preparations may also contain other therapeutic agents.

25

The following examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

30

EXAMPLE 1

1-(2-Deoxy-2-fluoro- β -D-arabinofuranosyl)thymine (1.5 g, 5.76 mmol) is dissolved in dry pyridine (15 ml) and
35 acetic anhydride (5 ml) is added. The mixture is stirred overnight at room temperature and is then concentrated in vacuo. The residue is chromatographed on a column of

1 silica gel G60 using n-hexano-ethyl acetate (1:2) as the
 eluent. Upon evaporation of the major UV-absorbing frac-
 tion, 1-(3, 5-di-O-acetyl-2-deoxy-2-fluoro- β -D-arabino-
 furanosyl)thymine (1.62 g, 82 %) is obtained as a
 5 colorless amorphous solid.

¹H NMR (CDCl₃) 1.94 (3H, s, Me), 2.13 (3H, s, Ac),
 2.17 (3H, s, Ac), 4.25 (1H, m, H-4'), 4.44 (2H, m, H-
 5'5"), 5.10 (1H, dd, H-2', J_{2',F} = 49.95, J_{1',2'} = 2.74
 10 Hz), 5.23 (1H, dd, H-3', J_{3',F} = 16.88, J_{2',3'} = 2.61),
 6.22 (1H, dd, H-1', J_{1',F} = 21.95, J_{1',2'} = 2.74), 7.33
 (1H, s, H-6), 9.91 (1H, s, NH, exchangeable).

Microanalysis (C₁₄H₁₇FN₂O₇). Calcd: C, 48.84; H, 4.98; N,
 15 8.14. Found: C, 48.98; H, 5.12; N, 8.08.

By following the same procedure but using the correspon-
 ding 2'-substituted nucleosides as starting materials,
 the following compounds are also prepared:

20

1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy- β -D-
 arabinofuranosyl)thymine.

1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy- β -D-
 arabinofuranosyl)thymine.

25

1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo- β -D-
 arabinofuranosyl)thymine.

1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro- β -D-
 ribofuranosyl)thymine.

30

1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy- β -D-
 ribofuranosyl)thymine.

1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy- β -D-
 ribofuranosyl)thymine.

1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo- β -D-
 ribofuranosyl)thymine.

35

1 EXAMPLE 2

A mixture of thymidine (0.50 g, 2.06 mmol) and tert-butyl-diphenylsilyl chloride (0.60 ml, 2.31 mmol) in dry
5 pyridine (10 ml) is stirred overnight at room temperature, and then concentrated in vacuo. The residue is dissolved in methylene chloride and the solution washed with water, dried over sodium sulfate and concentrated
10 in vacuo. The residue is crystallized from acetone-n-hexane to afford S'-0-tert-butyl-diphenylsilylthymidine (600 mg), mp 170-171 °C. An additional amount (150 mg) of the silylated product is obtained from the mother
liquor, giving a total yield of 76 %. ¹H MNR (CDCl₃)
1.09 (9H, s, t-Bu), 1.64 (3H, s, Me), 1.94-2.63 (2H, m,
15 H-2', 2"), 3.70-4.12 (3H, m, H-4', 5', 5''), 4.57 (1H, m
H-3'), 6.41 (1H, dd, H-1', J_{1',2'} = 7.93, J_{1',2''} = 6.10
Hz), 7.26-7.76 (11H, m, H-6 and Ph), 8.94 (1H, s, NH,
exchangeable).

20 Microanalysis (C₂₆H₃₂N₂O₅Si). Calcd: C, 64.97; H, 6.71;
N, 5.83. Found: C, 65.05; H, 6.75; N, 5.91.

By following the same procedure but using the corresponding 2'-substituted nucleoside analogs as starting materials,
25 the following compounds are also prepared:

1-(5'-0-tert-Butyl-diphenylsilyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine.

1-(5'-0-tert-Butyl-diphenylsilyl-2-chloro-2-deoxy-β-D-arabinofuranosyl)thymine.

1-(5'-0-tert-Butyl-diphenylsilyl-2-bromo-2-deoxy-β-D-arabinofuranosyl)thymine.

1-(5'-0-tert-Butyl-diphenylsilyl-2-deoxy-2-fluoro-β-D-ribofuranosyl)thymine.

15 1-(5'-0-tert-Butyl-diphenylsilyl-2-chloro-2-deoxy-β-D-ribofuranosyl)thymine.

- 1 1-(5'-0-tert-Butyldiphenylsilyl-2-bromo-2-deoxy- β -D-ribofuranosyl)thymine.

5 EXAMPLE 3.

To a solution of 5-methyluridine (3.00 g, 10.06 mmol) and tert-butyldiphenylsilyl chloride (6.50 ml, 25.0 mmol) in dry N,N-dimethylformamide (60 ml) is added
10 imidazole (3.00 g, 44.07 mmol), and the mixture is stirred overnight at room temperature. The solvent is removed in vacuo and the residue is partitioned between methylene chloride and water. The organic layer is separated, washed twice with water and concentrated in
15 vacuo. The residue is chromatographed over a column of silica gel G60 using carbon tetrachloride-acetone (10:1) as the eluent. Two fractions are obtained. Upon evaporation of the first fraction in vacuo and crystallization of the residue from carbon tetrachloride-petroleum
20 ether, 1-(2',5'-di-0-tert-butyldiphenyl- β -D-ribofuranosyl)thymine (3.78 g, 51 %) is obtained, mp 97-99°C.
¹H NMR (CDCl₃) 0.92 (9H, s, t-Bu), 1.11 (9H, s, t-Bu), 1.58 (3H, d, 5-Me, J_{Me,6} = 1.24 Hz), 3.73 (1H, dd, H-5', J_{5',5''} = 11.73, J_{4',5''} = 1.64), 3.91 (1H, dd, H-
25 5'', J_{5',5''} = 11.73, J_{4',5''} = 1.92), 4.18 (1H, m, H-4'), 4.39 (2H, m, H-2',3'), 6.20 (1H, m, H-1'), 6.78 (1H, d, H-6, J_{Me,6} = 1.24), 7.10-7.71 (20H, m, Ph), 7.81 (1H, broad s, NH, exchangeable).

30 Microanalysis (C₄₂H₅₀N₂O₆Si₂·2H₂O) Calcd: C, 65.21; H, 7.06; N, 3.63. Found: C, 65.20; H, 7.10; N, 3.44.

From the second fraction, 1-(3',5'-di-0-tert-butyldiphenylsilyl- β -D-ribofuranosyl)thymine (1.86 g, 25 %) is
35 obtained, after recrystallization from benzene-hexane, mp 86-89°C. ¹H NMR (CDCl₃) 0.96 (9H, s, t-Bu), 1.13 (9H, s, t-Bu), 1.49 (3H, s, 5-Me), 2.81 (1H, dd, H-5',

- 1 $J_{5',5''} = 11.66$, $J_{4',5'} = 1.92$, 3.54 (1H, dd, H-5'',
 $J_{5',5''} = 11.66$, $J_{4',5'} = 1.88$). 3.77 (1H, m, H-4'),
 $J_{5',5''} = 11.66$, $J_{4',5'} = 1.88$). 4.19 (1H, m, H-3'), 4.46 (1H, m, H-2'), 6.16 (1H, d, H-
1', $J_{1',2'} = 7.68$), 7.08-7.78 (21H, m, H-6 and Ph), 8.35
5 (1H, s, NH, exchangeable).

Microanalysis ($C_{42}H_{50}N_2O_6Si_2$) Calcd: C, 68.63; H, 6.80;
N, 3.81. Found: C, 68.74; H, 7.09; N, 3.65.

- 10 By following the same procedure but using 1-(β -D-
arabinofuranosyl)thymine as the starting material, 1-
(3',5'-di-O-tert-butyldiphenylsilyl- β -D-arabinofurano-
syl)thymine and 1-(2,5-di-O-tert-butyldiphenylsilyl- β -D-
arabinofuranosyl)thymine are also prepared.

15

EXAMPLE 4

- A mixture of 3',5'-di-O-acetylthymidine (4.50 g, 13.78
20 mmol) in carbon tetrachloride (900 ml) is refluxed under
nitrogen until a clear solution is obtained. A solution
of bromine (0.8 ml, 15.61 mmol) in carbon tetrachloride
(18 ml) is very slowly added to the refluxing solution
over a period of 2 to 3 hours, while the reaction mix-
25 ture is irradiated with a 500 watt UV lamp. After all
the bromine is added, nitrogen is bubbled through the
solution for 30 minutes to remove hydrogen bromide. The
solution is concentrated to dryness in vacuo. The crude
5-bromomethyl-uracil nucleoside intermediate thus ob-
30 tained is dissolved in anhydrous acetonitrile (50 ml)
and treated with powdered silver fluoride (8 g, 63.10
mmol) for 15 minutes with vigorous stirring at room
temperature. The precipitate is removed by filtration
and the filtrate is concentrated to dryness in vacuo.
35 The residue is dissolved in chloroform, washed successi-
vely with water and saline, dried over sodium sulfate
and concentrated to dryness. The residue is chromatogra-

- 1 phed on a column of silica gel G60 using n-hexane-ethyl acetate (1:1). Upon evaporation of the major fraction in vacuo and crystallization of the residue from methylene chloride-ether-petroleum ether, 1-(3',5'-di-O-acetyl- β -
 5 D-erythropentofuranosyl)-5-monofluoromethyluracil (1.5 g, 32 %) is obtained, mp 24-27° C. ¹H NMR (CDCl₃) δ 2.12 (6H, s, 3',5'-Ac), 2.24 (1H, m, H-2'), 2.57 (1H, dq, H-2'', J_{2',2''} = 14.27, J_{1',2''} = 5.77, J_{2'',3} = 2.06), 4.31 (3H, m, H-4',5',5''), 5.19 (2H, dd, CH F, J_{H,F} = 47.48, J_{H,H} = 3.29), 5.25 (1H, m, H-3'), 6.32 (1H, dd, H-1', J_{H,H} = 8.24, J_{1',2''} = 5.77), 7.69 (1H, d, H-6, J_{6,F} = 2.47).

- Microanalysis (C₁₄H₁₇FN₂O₇) Calcd: C, 48.84; H, 4.98; F, 5.52; N, 8.14. Found: C, 49.14; H, 5.21; F, 5.21; N, 7.87.

EXAMPLE 5

- 20 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro- β -D-arabinofuranosyl)thymine (170 mg, 0.49 mmol) is brominated by a procedure described in Example 4. The crude 5-bromomethyluracilnucleoside is dissolved in anhydrous tetra-
 25 hydrofuran (1 ml) and 0.5 M tetra-n-butylammonium fluoride in tetrahydrofuran (2 ml) is added. The mixture is stirred for 30 minutes at room temperature and then chromatographed on a silica gel G60 column using n-hexane-ethyl acetate (1:2) as the eluent. 1-(3,5-Di-O-acetyl-2-deoxy-2-fluoro- β -D-arabinofuranosyl)-5-Mono-
 30 fluoromethyluracil (22 mg, 12 %) is obtained after concentration of the nucleoside-containing fraction and crystallization of the residue from benzene; mp 109-110° C. ¹H NMR (CDCl₃) δ 2.12 (3H, s, Ac), 2.17 (3H, s, Ac), 4.26 (1H, m, H-4'), 4.46 (2H, m, H-5',5''), 5.13 (1H, dd, H-2', J_{2',F} = 50.22, J_{1',2'} = 2.74 Hz), 5.18 (2H, d, CH F, J_{H,F} = 47.74), 5.24 (1H, dd, H-3', J_{3',F} = 16.60,

1 $J_{2',3'} = 2.06$, 6.22 (1H, dd, H-1', $J_{1',F} = 21.40$,
 $J_{1',2'} = 2.74$), 7.73 (1H, broad s, H-6), 9.36 (1H, broad
 s, NH, exchangeable).

5 Microanalysis ($C_{14}H_{16}F_2N_2O_7$) Calcd: C, 46.41; H, 4.45;
 F, 10.49; N, 7.73. Found: C, 46.15; H, 4.51; F, 10.31;
 N, 7.75.

10 EXAMPLE 6

Crude 1-(5'-O-tert-butyldiphenylsilyl-2'-deoxy- β -D-erythropentofuranosyl)-5-monobromouracil (obtained by bromination of 5-O-tert-butyldiphenylsilylthymidine (120
 15 mg, 0.25 mmol) is dissolved in dry acetone (5 ml) and amberlyst A-26 (F) (0.5 g) is added. The mixture is vigorously stirred at room temperature four 1 hour and the resin is filtered and washed with acetone. The concentrated filtrate and washings are concentrated in
 20 vacuo and the residue chromatographed over a column of silica gel G60 using n-hexane-ethyl acetate (1:3). 1-(5'-O-tert-Butyldiphenylsilyl-2'-deoxy- β -D-erythropentofuranosyl)-5-monofluorouracil (26 mg, 21 %) is obtained in pure form after crystallization from n-hexane-
 25 methylene chloride, mp 129-131 °C. 1H NMR ($CDCl_3$) δ 1.04 (3H, s, Me in tBu), 1.08 (6H, s, 2Me in tBu), 1.96-2.62 (2H, m, H-2',2''), 3.75-4.19 (3H, m, H-4',5',5''), 4.80 (2H, d, CH F, $J_{H,F} = 47.92$ Hz), 6.22 (1H, dd, H-1',
 $J_{1',2'} = 5.76$, $J_{1',F} = 7.41$), 7.29-7.77 (10H, m, Ph),
 30 7.83 (1H, d, H-6, $J_{6,F} = 3.35$), 8.45 (1H, broad s, NH, exchangeable).

Microanalysis ($C_{26}H_{21}FN_2O_5Si$) Calcd: C, 62.63; H, 6.27;
 F, 3.81; N, 5.62. Found: C, 62.66; H, 6.36; F, 3.66; N,
 35 5.78.

- 1 The following 5-monofluoromethyluracil nucleosides are prepared by following the same procedures described in Example 4 and Example 6 but using the corresponding blocked nucleoside intermediates. When the silver fluoride-acetone combination as in Example 4 is used, the yields are 30 % - 55 %, whereas the Amberlyst A-26 (F⁻)-acetone procedure as in Example 6 gives the following products in 20 % - 40 % yields:
- 5
- 10 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-monofluoromethyluracil
1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil
1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil
- 15 1-(5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-monofluoromethyluracil.
1-(5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil.
- 20 1-(5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-β-D-arabinofuranosyl)-5-monofluoromethyluracil.
1-(2',3',5'-Tri-O-acetyl-β-D-arabinofuranosyl)-5-monofluoromethyluracil
1-(2',5'-Di-O-tert-butyldiphenylsilyl-β-D-arabinofuranosyl)-5-monofluoromethyluracil
- 25 1-(3',5'-Di-O-tert-butyldiphenylsilyl-β-D-arabinofuranosyl)-monofluoromethyluracil
3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-5-monofluoromethyluridine
- 30 3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-5-monofluoromethyluridine
3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-5-monofluoromethyluridine
5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5-monofluoromethyluridine.
- 35 5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-5-monofluoromethyluridine.

- 1 5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-
monofluoromethyluridine.
2',3',5'-Tri-0-acetyl-5-monofluoromethyluridine
2',5'-Di-0-tert-butyldiphenylsilyl-5-
5 monofluoromethyluridine
3',5'-Di-0-tert-butyldiphenylsilyl-5-
monofluoromethyluridine

By following the procedure of Example 5 but using the
10 corresponding acetylated nucleosides as the interme-
diates, the following nucleosides are also prepared in
10 % - 20 % yield.

- 1-(3',5'-Di-0-acetyl-2'-chloro-2'-deoxy-β-D-
15 arabinofuranosyl)-5-monofluoromethyluracil
1-(3',5'-Di-0-acetyl-2'-bromo-2'-deoxy-β-D-
arabinofuranosyl)-5-monofluoromethyluracil
1-(2',3',5'-Tri-0-acetyl-β-D-arabinofuranosyl)-5-
monofluoromethyluracil
20 3',5'-Di-0-acetyl-2'-deoxy-5-monofluoromethyluridine
3',5'-Di-0-acetyl-2'-deoxy-2'-fluoro-5-
monofluoromethyluridine
3',5'-Di-0-acetyl-2'-chloro-2'-deoxy-5-
monofluoromethyluridine
25 3',5'-Di-0-acetyl-2'-bromo-2'-deoxy-5-
monofluoromethyluridine
2',3',5'-Tri-0-acetyl-5-monofluoromethyluridine.

30 EXAMPLE 7

A solution of bromine (0.118 ml, 2.30 mmol) in carbon
tetrachloride (2 ml) is slowly blown with a stream of
dry nitrogen into a refluxing solution of 1-(5'-0-tert-
35 butyldiphenylsilyl-2'-deoxy-2'-fluoro-β-D-arabinofurano-
syl)thymine (498 mg, 1 mmol) in carbon tetrachloride
while irradiated with a UV light. After 30 minutes, when

- 1 all the bromine is added, nitrogen is bubbled through the solution for a further 15 minutes to remove the hydrogen bromide.
- 5 The solution is concentrated to dryness in vacuo and the residue dissolved in dry acetonitrile (100 ml). Finely pulverized silver fluoride (1.0 g, 7.88 mmol) is added to the solution and the mixture is stirred vigorously for 15 minutes at room temperature. The mixture is
- 10 filtered and the filtrate is concentrated in vacuo. The residue is dissolved in chloroform, washed with water and saline, dried over sodium sulfate and concentrated in vacuo. The residue is chromatographed on a column of silica gel G60 using methylene chloride - tetrahydro-
- 15 furan (20:1 to 10:1) as the eluent. The UV absorbing fraction eluted with 10:1 methylene chloride - tetrahydrofuran is concentrated and the residue crystallized from methylene chloride - petroleum ether. 1-(5'-O-tert-Butyldiphenylsilyl)-2'-deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-difluoromethyluracil (80 mg, 15 %) is obtained,
- 20 mp 132-134 °C. ¹H NMR (CDCl₃) δ 1.08 (9H, s, tBu), 3.75-4.09 (3H, m, H-4', 5', 5''), 4.55 (1H, dq, H-3', J_{2',3'} = 22.23, J_{3',4'} = 0.82, J_{3',4'} = 0 Hz), 5.05 (1H, dq, H-2', J_{2',3'} = 51.05, J_{1',2'} = 3.30, J_{2',3'} = 0.82), 6.77
- 25 (1H, dd, H-1', J_{1',2'} = 19.49, J_{1',2'} = 3.30) 6.56 (1H, t, CHF₂, J_{H,F} = 54.75). 7.23-7.81 (10H, m, Ph), 7.87 (1H, d, H-6, J_{6,F} = 1.37), 8.79 (1H, broad s, NH, exchangeable).

Microanalysis (C₂₆H₂₉F₃N₃O₅Si) Calcd: C, 58.41; H, 5.47; F, 10.66; N, 5.24. Found: C, 58.58; H, 5.69; F, 10.49; N, 5.19.

By following the same procedure but using the corresponding protected nucleosides, the following 5-difluoromethyluracil nucleosides are prepared:

- 1 1-(3',5'-Di-O-acetyl-2'-deoxy- β -D-erythropentofuranosyl)-5-difluoromethyluracil
1-(2',5'-Di-O-acetyl-2'-deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-difluoromethyluracil
- 5 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil
1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil
1-(2',3',5'-Tri-O-acetyl- β -D-arabinofuranosyl)-5-
- 10 difluoromethyluracil
1-(5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil
1-(5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil
- 15 1-(2',5'-Di-O-tert-butyldiphenylsilyl- β -D-arabinofuranosyl)-5-difluoromethyluracil
1-(3',5'-Di-O-tert-butyldiphenylsilyl- β -D-arabinofuranosyl)-5-difluoromethyluracil
3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-5-
- 20 difluoromethyluridine
3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-5-difluoromethyluridine
3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-5-difluoromethyluridine
- 25 2',3',5'-Tri-O-acetyl-5-difluoromethyluridine
5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5-difluoromethyluridine
5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-5-difluoromethyluridine
- 30 5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-difluoromethyluridine
2',5'-Di-O-tert-butyldiphenylsilyl-5-difluoromethyluridine
3',5'-Di-O-tert-butyldiphenylsilyl-5-
- 35 difluoromethyluridine.

1 EXAMPLE 8

1-(5'-0-tert-Butyldiphenylsilyl-2'-deoxy- β -D-erythro-pentofuranosyl)-5-monofluoromethyluracil (440 ml, 0.88 mmol) is dissolved in dry tetrahydrofuran (4 ml) and 0.5 M tetra-n-butylammonium fluoride in tetrahydrofuran (2.2 ml) is added. The mixture is stirred at room temperature for 90 minutes and then concentrated in vacuo. The residue is chromatographed on a silica gel G60 column using methylene chloride-tetrahydrofuran (1:1) as the eluent. After concentration of the UV absorbing fraction, the residue is crystallized from acetone to give 2'-deoxy-5-monofluoromethyluridine, 143 mg (63 %), mp 140° C (dec). ¹H MNR (d₂-acetone) δ 2.21 (2H, m, H-2', 2''), 3.71 (2H, m, H-5', 5''), 3.88 (1H, apparent dd, H-4', J_{3,4'} = 3.16, J_{4',5'} = 6.17, J_{4',5''} = 0 Hz), 4.39 (1H, m, H-3'), 4.96 (2H, d, CH₂F, J_{H,F} = 49.12), 6.20 (1H, apparent t, H-1', J_{1',2'} = J_{1',2''} = 6.59, 8.23 (1H, d H-6, J_{6,F} = 4.12).

Microanalysis (C₁₀H₁₃FN₂O₅) Calcd: C, 46.16; H, 5.03; F, 7.30; N, 10.76. Found: C, 46.28; H, 5.31; F, 7.16; N, 10.58.

By following the same procedure but using the corresponding silylated nucleoside intermediates, the following 5-(partially fluorinated) methyluracil nucleosides are prepared:

1-(2'-Deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-monofluoromethyluracil

1-(2'-Chloro-2'-deoxy- β -D-arabinofuranosyl)-5-monofluoromethyluracil

1-(2'-Bromo-2'-deoxy- β -D-arabinofuranosyl)-5-monofluoromethyluracil

1-(β -D-arabinofuranosyl)-5-monofluoromethyluracil

- 1 2'-Deoxy-2'-fluoro-5-monofluoromethyluridine
2'-Chloro-2'-deoxy-5-monofluoromethyluridine
2'-Bromo-2'-deoxy-5-monofluoromethyluridine
5-Monofluoromethyluridine
- 5 1-(2'-Deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-
difluoromethyluracil
1-(2'-Chloro-2'-deoxy- β -D-arabinofuranosyl)-5-
difluoromethyluracil
1-(2'-Bromo-2'-deoxy- β -D-arabinofuranosyl)-5-
10 difluoromethyluracil
1-(β -D-Arabinofuranosyl)-5-difluorouracil
2'-Deoxy-5-difluoromethyluridine
5-Difluoromethyluridine
2'-Deoxy-2'-fluoro-5-difluoromethyluridine
- 15 2'-Chloro-2'-deoxy-5-difluoromethyluridine
2'-Bromo-2'-deoxy-5-difluoromethyluridine.

The results of antiviral assay of some representative nucleosides are given in Table I.

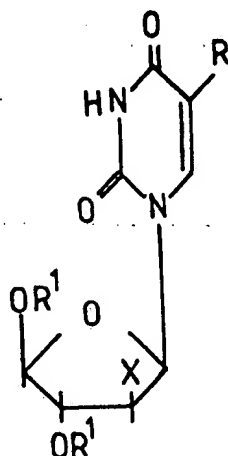
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1 TABLE I.

Antiherpes Activity of α -fluorinated thymine nucleosides

Inhibitory Concentration (μ M) Toxic Concentration (μ M)

R R1 X HSV-1 HSV-2

	CH ₂ F	H	H	>100	>100	1,000
20	CH ₂ F	Ac	H	>100	>100	1,000
	CHF ₂	H	H	1.40	1.66	1,000
	CHF ₂	Ac	H	17.0	25.1	1,000
	CH ₂ F	H	F	0.21	0.18	1,000
	CH ₂ F	Ac	F	2.46	5.19	1,000
25	CHF ₂	H	F	0.48	1.04	1,000
	CHF ₂	Ac	F	0.71	2.16	1,000
	(FMAU) CH ₃	H	F	0.10	0.05	1,000
	CH ₃	Ac	F	0.44	1.23	1,000

30

35

- 1 Each of the nucleosides was initially dissolved in a
diluent containing 60 % propylene glycol and 10 % EtOH;
subsequent dilutions used maintenance culture medium.
Agents were assessed at tenfold dilutions with final
5 concentrations ranging from 10,000 to 0.01 micromolar.

Confluent human foreskin monolayers were maintained in
96-well microtiter plates using Eagle's Minimal Essen-
tial Medium supplemented with 2 % fetal bovine serum,
10 antibiotics and glutamine using standard methods.
Prior to virus inoculation, the medium was removed from
each well and replaced with 100 μ l of agent diluted in
maintenance medium with differing concentrations in each
horizontal row, beginning with the highest concentration
15 in the upper row, with subsequent tenfold dilutions in
the next rows and the last (control) row fed with agent-
free maintenance medium. The virus inocula were then
added, suspended in 100 μ l of maintenance medium. A
high-dose inoculum which induced nearly confluent (100
20 %) cytopathic effect (CPE) two days later was added to
the first five vertical columns of the plate (1-5) and,
similarly, a low-dose inoculum inducing approximately 50
% CPE in each well two days later was added to the next
five vertical columns (6-10). To the last two columns,
25 virus-free medium was added to serve as uninfected con-
trol wells in order to assess direct cellular cytotoxi-
city at each agent dilution. The plates were then incu-
bated at 36.9⁰ C in 9 % CO₂ in air for two days, at
which time they were read.

30

The cytopathology of each well was read using an inver-
ted microscope and scored from 0 to 4 (0 = no CPE and 4
= > 95 % CPE); for marginal or equivocal readings a + or
- is affixed to each score. For calculation of the
35 inhibitory concentrations (IC) of agents and interpola-
ting between dilutions of agents, each well reading was
converted to a numerical score (4 = 40, 4- = 37, 3+ = 33;

1 3 = 30, etc). The mean score of each five wells in a row
Receiving a given agent dilution and virus inoculum was
then calculated and compared with an appropriate control
row receiving no agent. Significant inhibition was jud-
5 ged to occur when the mean well score at a given agent
concentration was lower than the mean value of the
control row by 10 scoring units. When the value fell
between two rows, simple arithmetic interpolation was
done to calculate the agent concentrate at the point on
10 a slope between the mean scores in the rows above and
below this point. The IC values of each agent using the
high and low virus inocula were then averaged yielding a
final mean IC which was expressed as a micromolar drug
concentration.

15 Although α,α,α -trifluorothymidine (Formula IV, $R = CF_3$,
 $X = H$, $R^1 = H$) is reported to be antiherpetic and very
cytotoxic, the α,α -difluoro analog (Formula IV, $R =$
 CHF_2 , $X = H$ or Ac , $R^1 = H$) showed very potent antiherpes
20 activity without serious cytotoxicity. In the FMAU se-
ries, fluorination of the 5-methyl group does not alter
the antiherpetic activity significantly.

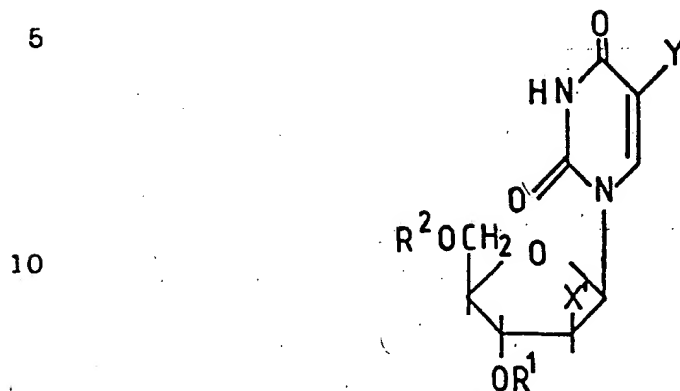
The acetylated derivatives may act as masked precursors
25 which may be saponified by esterases to release active
free nucleosides. The ^{18}F -labeled nucleosides which can
be prepared by the method we developed may be useful for
diagnosis of herpes encephalitis, employing Positron
Emission Tomography scanning.

30

35

1 CLAIMS :

1. Pyrimidine nucleosides having the formula



wherein:

- X or X' is H
- 15 X or X' is a halogen, pseudohalogen or OR³ wherein
R³ is H, acyl or trisubstituted-silyl;
- Y is CH₁F or CHF₂;
- R¹ and R² are the same or different and are H, acyl
or trisubstituted-silyl.
- 20
2. Nucleosides of Claim 1 selected from the group of:
- 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-
arabinofuranosyl)thymine
- 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-
25 arabinofuranosyl)thymine
- 1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-
arabinofuranosyl)thymine
- 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo-β-D-
arabinofuranosyl)thymine
- 30 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-
ribofuranosyl)thymine
- 1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-
ribofuranosyl)thymine
- 1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-
35 ribofuranosyl)thymine
- 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-iodo-β-D-
ribofuranosyl)thymine.

- 1 3. Nucleosides of Claim 1 selected from the group of:
5'-0-tert-Butyldiphenylsilylthymidine
1-(5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-
β-D-arabinofuranosyl)thymine
5 1-(5'-0-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-
β-D-arabinofuranosyl)thymine
1-(5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-
β-D-arabinofuranosyl)thymine
1-(2',5'-Di-0-tert-butylidiphenylsilyl-β-D-arabino-
10 furanosyl)thymine
1-(3',5'-Di-0-tert-butylidiphenylsilyl-β-D-arabino-
furanosyl)thymine
1-(5'-0-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-
β-D-ribofuranosyl)thymine
15 1-(5'-0-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-
β-D-ribofuranosyl)thymine
1-(5'-0-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-
β-D-ribofuranosyl)thymine
1-(2',5'-Di-0-tert-butylidiphenylsilyl-β-D-ribofura-
20 nosyl)thymine
1-(3',5'-Di-0-tert-butylidiphenylsilyl-β-D-ribofura-
nosyl)thymine.
4. Nucleosides of Claim 1 selected from the group of:
25 1-(3',5'-Di-0-acetyl-2'-deoxy-2'-fluoro-β-D-
arabinofuranosyl)-5-monofluoromethyluracil
1-(3',5'-Di-0-acetyl-2'-chloro-2'-deoxy-β-D-
arabinofuranosyl)-5-monofluoromethyluracil
1-(3',5'-Di-0-acetyl-2'-bromo-2'-deoxy-β-D-
30 arabinofuranosyl)-5-monofluoromethyluracil
1-(2',3',5'-Tri-0-acetyl-β-D-arabinofuranosyl)-5-
monofluoromethyluracil
3',5'-Di-0-acetyl-2'-deoxy-5-monofluoromethyluridine
3',5'-Di-0-acetyl-2'-deoxy-2'-fluoro-5-
35 monofluoromethyluridine
3',5'-Di-0-acetyl-2'-chloro-2'-deoxy-5-
monofluoromethyluridine

- 1 3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-5-monofluoromethyluridine
2',3',5'-Tri-O-acetyl-5-monofluoromethyluridine.
- 5 5. Nucleosides of Claim 1 selcted from the group of:
1-(5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-
β-D-arabinofuranosyl)-5-monofluoromethyluracil
1-(5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-
β-D-arabinofuranosyl)-5-monofluoromethyluracil
10 1-(5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-
β-D-arabinofuranosyl)-5-monofluoromethyluracil
1-(2',5'-Di-O-tert-butylidiphenylsilyl-β-D-
arabinofuranosyl)-5-monofluoromethyluracil
1-(3',5'-Di-O-tert-butylidiphenylsilyl-β-D-
15 arabinofuranosyl)-5-monofluoromethyluracil
5'-O-tert-Butyldiphenylsilyl-2'-deoxy-5-
monofluormethyluridine
5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5-
monofluoromethyluridine
20 5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-5-
monofluoromethyluridine
5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-
monofluoromethyluridine
2',5'-Di-O-tert-butylidiphenylsilyl-5-
25 monofluoromethyluridine
3',5'-Di-O-tert-butylidiphenylsilyl-5-
monofluoromethyluridine.
6. Nucleosides of Claim 1 selceted from the group of:
30 1-(3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-β-D-
arabinofuranosyl)-5-difluoromethyluracil
1-(3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-β-D-
arabinofuranosyl)-5-difluoromethyluracil
1-(3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-β-D-
35 arabinofuranosyl)-5-difluoromethyluracil
3',5'-Di-O-acetyl-2'-deoxy-5-difluoromethyluridine

- 1 3',5'-Di-O-acetyl-2'-deoxy-2'-fluoro-5-difluoromethyluridine
3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-5-difluoromethyluridine
5 3',5'-Di-O-acetyl-2'-bromo-2'-deoxy-5-difluoromethyluridine
2',3',5'-Tri-O-acetyl-5-difluoromethyluridine.
7. Nucleosides of Claim 1 selected from the group of:
10 1-(5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-difluoromethyluracil
1-(5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil
1-(5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil
15 1-(2',5'-Di-O-tert-butyl-diphenylsilyl- β -D-arabinofuranosyl)-5-difluoromethyluracil
1-(3',5'-Di-O-tert-butyl-diphenylsilyl- β -D-arabinofuranosyl)-5-difluoromethyluracil
20 5'-O-tert-Butyldiphenylsilyl-2'-deoxy-5-difluoromethyluridine
5'-O-tert-Butyldiphenylsilyl-2'-deoxy-2'-fluoro-5-difluoromethyluridine
5'-O-tert-Butyldiphenylsilyl-2'-chloro-2'-deoxy-5-difluoromethyluridine
25 5'-O-tert-Butyldiphenylsilyl-2'-bromo-2'-deoxy-5-difluoromethyluridine
2',5'-Di-O-tert-butyl-diphenylsilyl-5-difluoromethyluridine
30 3',5'-Di-O-tert-butyl-diphenylsilyl-5-difluoromethyluridine.
8. Nucleosides of Claim 1 selected from the group of:
35 1-(2'-Deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-monofluoromethyluracil
1-(2'-Chloro-2'-deoxy- β -D-arabinofuranosyl)-5-monofluoromethyluracil

- 1 1-(2'-Bromo-2'-deoxy- β -D-arabinofuranosyl)-5-monofluoromethyluracil
1-(β -D-arabinofuranosyl)-5-monofluoromethyluridine
5-Monofluoromethyluridine
- 5 2'-Deoxy-5-monofluoromethyluridine
2'-Deoxy-2'-fluoro-5-monofluoromethyluridine
2'-Deoxy-2'-chloro-5-monofluoromethyluridine
2'-Deoxy-2'-bromo-5-monofluoromethyluridine.
- 10 9. Nucleosides of Claim 1 selected from the group of:
1-(2'-Deoxy-2'-fluoro- β -D-arabinofuranosyl)-5-difluoromethyluracil
1-(2'-Chloro-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil
- 15 1-(2'-Bromo-2'-deoxy- β -D-arabinofuranosyl)-5-difluoromethyluracil
1-(β -D-arabinofuranosyl)-5-difluoromethyluracil
5-Difluoromethyluridine
2'-Deoxy-5-difluoromethyluridine
- 20 2'-Deoxy-2'-fluoro-5-difluoromethyluridine
2'-Chloro-2'-deoxy-5-difluoromethyluridine
2'-Bromo-2'-deoxy-5-difluoromethyluridine.
10. Pharmaceutical composition comprising an effective
25 amount of nucleoside of formula defined in Claim 1.

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